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Contribution of diet and other factors to the observed levels of selected perfluoroalkyl acids in serum among US children aged 3-11 years☆

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ABSTRACT

Data from National Health and Nutrition Examination Survey for 2013–2014 for children aged 3–11 years (N = 639) were analyzed to evaluate the contribution of diet and other factors in variability associated with the observed levels of seven perfluoroalkyl acids in serum, namely, 2(N-methyl-perfluorooctane sulfonamide) acetic acid (MPAH), perfluorodecanoic acid (PFDE), perfluorononanoic acid (PFNA), perflurorohexane sulfonic acid (PFHxS), linear isomer of PFOA (NPFOA), linear isomer of PFOS (NPFOS), and monomethyl isomer of PFOS (MPFOS). Diet accounted for a low of 18.6% of the total explained variance in the adjusted levels of NPFOA and a high of 72.3% for PFNA. Consumption of meat other than fish and poultry was associated with increased levels of NPFOS (β = 0.00035, $p < 0.01$) and MPFOS (β = 0.00027, $p = 0.02$). However, consumption of fish was associated with decreased levels of PFDE (β = − 0.00058, $p = 0.01$). Consumption of eggs was associated with higher levels of PFDE (β = 0.00105, $p = 0.04$). Higher levels of PFHxS were associated with consumption of fruits and juices (β = 0.00019, $p = 0.03$). Exposure to environmental tobacco smoke in indoor environments other than home was associated with 12.6% increase in the levels of NPFOA. Boys had higher adjusted geometric mean (AGM) than girls for MPAH (0.88 vs. 0.70 ng/mL, $p = 0.04$) and NPFOS (2.73 vs. 2.27 ng/mL, $p = 0.04$). Non-Hispanic white had higher AGMs than Hispanics for MPAH (0.15 vs. 0.07, $p < 0.01$), for NPFOA (1.98 vs. 1.64 ng/mL, $p < 0.01$), and MPFOS (1.39 vs. 1.18 ng/mL, $p = 0.03$). Non-Hispanic white also had higher AGM than non-Hispanic Asians and others for PFHxS (0.99 vs. 0.63 ng/mL, $p < 0.01$) and NPFOA (1.98 vs. 1.53 ng/mL, $p < 0.01$).

1. Introduction

Perfluoroalkyl acids (PFAA), used in a wide variety of consumer products (Okada et al., 2013), are present everywhere. Selected PFAAs have been found to be present in water sediments (Wang et al., 2017), tap water (Lu et al., 2017), and agricultural soil and grains near industrial parks (Liu et al., 2017a). They have been detected in maternal serum samples (Bjerregaard-Olesen et al., 2017), breast milk (Cariou et al., 2015), and follicular fluids (Petro et al., 2014; McCoy et al., 2017). Adverse effects of prenatal exposure to PFAAs have been investigated by quite a few researchers (Alkhalawi et al., 2016; Kobayashi et al., 2017; Callan et al., 2016; Goudarzi et al., 2016; Okada et al., 2013). Breast feeding has been considered to be an excretion route for mothers (Cariou et al., 2015; Mondal et al., 2014). Exposure to PFAAs have been reported to adversely affect glomerular filtration rate and serum uric acid levels among adolescents aged 12–19 years (Kataria et al., 2015), clinical measures of reproductive health (McCoy et al., 2017), glycemic health (Lin et al., 2009), cardiovascular disease (Shankar et al., 2012), levels of total and non-high-density cholesterol (Nelson et al., 2010), and thyroid homeostasis (Ji et al., 2012; Lopez-Espinosa et al., 2012; Knox et al., 2011; Lin et al., 2012; Melzer et al., 2010; Jain, 2013).

Exposure to PFAAs can occur via contaminated food (Ostertag et al., 2009; Schuetze et al., 2010), food packaging and non-stick cookware (Tittlemier et al., 2006), water (Holzer et al., 2008), indoor air (https://www.atsdr.cdc.gov/pfc/sources_of_exposure.html) and indoor and outdoor dust (Fromme et al., 2009; Kubwabo et al., 2005). Infants can be exposed to PFAAs via breast milk (Cariou et al., 2015). Occupational exposure to PFAAs and subsequent transfer to family members has been documented by Fu et al. (2015). Makey et al. (2017) investigated the possibility of airborne PFAA precursors as a source of exposure to PFAAs in 50 maternal sera samples collected in 2007–2008 from participants in Vancouver, Canada.

PFAAs are used as multi-purpose surfactants or water/oil repellents (Lu et al., 2017). Some of the major PFAAs are: perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate

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(PFHxS), and perfluorononanoic acid (PFNA). Elimination half-life of PFOS, PFOA, and PFHxS in serum among humans is 5.4 years, 3.8 years, and 8.5 years respectively (Olsen et al., 2007) and as such, they bio-accumulate over time. Bio-accumulative potential of PFHxS and PFOS was found to be higher than other PFAAs (Fu et al., 2015).

Jain (2014a) used data from NHANES for the period 2003–2008 and contribution of diet and selected risk factors on the serum levels of PFOA, PFOS, PFHxS, and PFNA among US population aged > = 12 years was investigated. Dietary factors accounted for 10.4–21.2% of the explained variability depending on the PFAA. In a Canadian study (Tittlemier et al., 2007), diet was found to account for more than 60% of the total exposure to PFAAs. In an intake study in the population of Flanders, Belgium (Cornelis et al., 2012), dietary intake including from vegetables dominated total intake of PFOA and PFOS. Liu et al. (2017b) reported fish, shellfish, red meat and poultry to be associated with increased PFAAs concentrations in plasma, whereas grains and soy products were found to be inversely associated with PFAAs.

While NHANES data on PFAAs for those aged > = 12 years have been released in the public domain since 2003–2004 NHANES cycle, it was only for 2013–2014 that PFAA data for children aged 3–11 were released. Consequently, this study was undertaken to assess the contribution of diet and demographic factors to the observed levels of selected PFAAs in serum.

2. Materials and methods

2.1. Availability of data for PFAASs

Data for children aged 3–11 years were available for observed levels of 14 PFAAs in serum (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SSPFAC_H.htm), namely, perfluorooctane sulfonamide (PFSA), 2(N-methyl-perfluorooctane sulfonamide) acetic acid (MPAH), 2(N-ethyl-perfluorooctane sulfonamide) acetic acid (EPAH), perfluorodecanoic acid (PFDE), perflurorbutane sulfonic acid (PFBS), perfluoroheptanoic acid (PFHP), PFNA, perfluoroundecanoic acid (PFUA), perfluorododecanoic acid (PFDO), PFHxS, linear isomer of PFOA (NPFOA), branch isomer of PFOA (BPFOA), linear isomer of PFOS (NPFOS), and monomethyl isomer of PFOS (MPFOS). However, percent observations at or above the limit of detection for EPAH, PFBS, PFDO, PFHP, PFSA, PFUA, and BPFOA were too low (Table 1) to do a meaningful data analysis. Consequently, data were analyzed for seven PFAAs, namely, MPAH, MPFOS, NPFOA, NPFOS, PFDE, PFHxS, and PFNA.

Table 1
Percent observations at or above the limit of detection with 95% confidence intervals for selected perfluoroalkyl acids and substances (PFAAs) for children aged 3–11 years. Data from National Health and Nutrition Examination Survey 2013–2014.

PFAS	> = LOD (95% CI)
2(N-ethyl-perfluorooctane sulfonamido) acetic acid	3.4 (1.1 – 5.8)
2(N-methyl-perfluorooctane sulfonamido) acetic acid[a]	53.2 (42.8 – 63.6)
Monomethyl branch isomers of PFOS[a]	100 (100 – 100)
Linear perfluorooctanoate[a]	99.8 (99.3 – 100.3)
Linear perfluorooctane sulfonate[a]	100 (100 – 100)
Perfluorobutane sulfonic acid	4.9 (1.9 – 8.0)
Pefluorodecanoic acid[a]	47.3 (39.1 – 55.5)
Perflurododecanoic acid	0 (0 – 0)
Perfluoroheptanoic acid	19.2 (12.8 – 25.6)
Perfluorohexane sulfonic acid[a]	99.9 (99.7 – 100.1)
Perfluorononanoic acid[a]	99.9 (99.6 – 100.1)
Perfluorooctane sulfonmide	3.2 (1.0 – 5.5)
Perfluoroundecanoic acid	27.5 (21.5 – 33.5)
Branch isomers of perfluorooctanoate	28.2 (20.3 – 36.1)

[a] Selected for data analysis.

Table 2
Unweighted sample sizes by gender and race/ethnicity used in unadjusted and adjusted analyses.

	Unadjusted Analysis		Adjusted Analysis	
	N	%	N	%
Total	639	100	526	100.0
Boys	343	53.7	285	54.2
Girls	296	46.3	241	45.8
Non-Hispanic White	166	26.0	138	26.2
Non-Hispanic Black	160	25.0	135	25.7
Hispanic	220	34.4	180	34.2
Non-Hispanic Asian	49	7.7		
Other	44	6.9		
Non-Hispanic Asian and others			73	13.9

The total sample size available for analysis was 639 (Table 2) but because of the missing values for independent variables, the total sample size available for doing the adjusted analyses was limited to 526 (Table 2).

2.2. Data on exposure to environmental tobacco smoke

Data on exposure to environmental tobacco smoke (ETS) inside children's home (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SMQFAM_H.htm) were available for two variables, namely, number of persons smoking inside the home and if so, number of days they smoked inside home during the last 7 days. A variable ETS_H was generated to indicate the exposure to ETS at home (no, yes). Data were also available for exposure to ETS (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SMQSHS_H.htm) during the last 7 days when inside a restaurant, taking ride in a car, when inside somebody else's home, and when in another indoor area. A variable indicating exposure to ETS (no, yes) from one or more other indoor environments was generated for use in the analysis.

2.3. Data on dietary variables

Jain (2014a) used data from NHANES individual food files for the survey period 2003–2008 to evaluate the association of 17 food groups with the levels of selected PFAAs. These food groups were: cheese, milk and milk products other than cheese, fish, poultry, eggs, dry beans, grain products, fruits and juices, dark green vegetables, tomatoes, vegetables other than tomatoes and dark green vegetables, fats and oils, sugars and sweets, non-alcoholic beverages, alcoholic beverages, and non-carbonated water. For this study, since alcoholic beverages were not an applicable choice, data in grams consumed for other 16 food groups were used to assess the association between consumption of these foods with 7 PFAAs listed above. Data were available at https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/DR1IFF_H.htm. Data on total intake (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/DR1TOT_H.htm) of calories, fats, and caffeine during the last 24 h were also used.

2.4. Treatment of observations below the limit of detection (LOD)

When percent observations > = LOD are at least 60%, all observation below LOD are usually substituted as LOD/Sqrt(2) as proposed by Hornung and Reed (1990). However, depending up on the percent observations below the LOD, substituting observations below LOD as LOD/Sqrt(2) may adversely affect estimation of location and dispersion parameters (Jain et al., 2008). Instead, use of maximum likelihood procedure with 5 imputations as proposed by Lubin et al. (2004) was recommended by Jain et al. (2008) and Jain and Wang (2008) when the sample size was at least 100 and percent observations below LOD were < 70%. Consequently, a decision was made to use maximum likelihood procedure as proposed by Lubin et al. (2004) with

Table 3
Contribution of various independent variables in explaining variability in the dependent variability. Data from National Health and Nutrition Examination Survey 2013–2014.

Dependent variable	R^2 in % when independent variables in the models were:		
	Demographic	Demographic + exposure to environmental tobacco smoke	Demographic + exposure to environmental tobacco smoke + dietary
2(N-methyl-perfluorooctane sulfonamido) acetic acid (MPAH)	6.9	7.2	12.8
Pefluorodecanoic acid (PFDE)	3.4	3.8	8.5
Perfluorononanoic acid (PFNA)	3.0	3.1	11.2
Perfluorohexane sulfonic acid (PFHxS)	7.0	7.5	14.2
Linear isomer of perfluorooctanoate (NPFOA)	9.1	9.6	11.8
Linear isomer of perfluorooctane sulfonate (NPFOS)	5.3	5.6	14.2
Monomethyl branch isomers of PFOS (MPFOS)	7.8	8.3	11.3

5 imputations to estimate all observations below the LOD for this study.

2.5. Database generation

NHANES data for 2013–2014 for children aged 3–11 years on demographics, body measures, PFAAs, ETS exposure, and dietary intake were downloaded and match merged. Since body mass index (BMI), itself, is not an appropriate measure of obesity for children, BMI percentiles (BMI PCT) based on Center for Disease Control's growth charts (Kuczmarski et al., 2002) were computed by using SAS software developed by Disease Control and Prevention (CDC) (https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm). Data on a total of 639 participants were available for analysis. Sample sizes by gender and race/ethnicity are given in Table 2. However, data on 113 out of 639 participants were missing for all dietary variables and as such they could not be used in the adjusted analysis. In order to have adequate sample size for each racial/ethnic category, data on non-Hispanic Asians and other unclassified race/ethnicity were merged together to form a new race/ethnic category. Sample size data for adjusted analysis are also given in Table 2.

2.6. Software and statistical analysis

University Edition SAS software (www.sas.com) was used to analyze all data for this study. Specifically, SAS Procs FREQ, SURVEYMEANS, and SURVEYREG were used to do univariate as well as multivariate analyses. Multivariate analyses included fitting a linear regression model for each of the seven PFAAs. Dependent variable used in each model was the log10 transformed values of each of the seven PFAASs. All models included gender (boys, girls), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanics, non-Hispanic Asians and other unclassified race/ethnicities) as categorical independent variables, and age, age^2, BMI percentile, poverty income ratio, fasting time in hours, exposure to ETS at home or ETS_H (no coded as 0 and yes coded as 1), and exposure to one or more other indoor environment ETS (no coded as 0 and yes coded as 1) were used as continuous variables. Dietary variables consumption in grams for each of the 16 food groups and total caffeine, calorie, and fat intake were also used in the model. A 3-step analysis was attempted to account for the contribution of various independent variables. In the first step, variables gender, race/ethnicity, age, age^2, BMI percentile, poverty income ratio, and fasting time in hours were entered into the models and their contribution as R^2 in percent was noted. In the second step of the model fitting, contribution of exposure to ETS was noted by adding ETS and ETS_H into the models. In the final step, all dietary variables were entered into the models as independent variables.

The reason for use of age^2 in the models as an independent variable was to be able to investigate the possible non-linear association between age and PFAAs. Usually, dichotomous variables like ETS and ETS_H are used as categorical independent variables in the models. However, inclusion of too many categorical variables in an investigation where sample size is limited as it was for this study, may lead to empty data cells. In order to avoid this, ETS and ETS_H were used as ordinal continuous variables.

During the analysis, it was found that there was very high correlation of > 0.90 between total caloric and total fat intake. This could have the potential to result in multicollinearity in the model fitting. To solve this issue, two alternate models were fitted for each PFAA. The first alternate model included only total caloric intake in the model and the second alternate model included only the total fat intake in the model.

3. Results

Contribution of variables entered into the models during the first step of the 3-step statistical analysis varied from 3.0% for the models for PFNA to 9.1% for the model for NPFNA (Table 3). Entering variables indicating exposure to ETS added as little as 0.1% for the model for PFNA to as much as 0.5% for the models for PFHxS, NPFOA, and MPFOA (Table 3). Contribution of dietary variables was as little as 2.2% for the model for NPFOA and as high as 8.6% for the model for NPFOS.

Adjusted geometric means (AGM) presented below and anywhere else in the text means they have been adjusted for all other variables in the model. For example, AGMs for males and females presented below and anywhere else in the text mean they have been adjusted for the effects of race/ethnicity, age, age^2, BMI percentile, poverty income ratio, fasting time, ETS, ETS_H, and all dietary variables.

3.1. Univariate analysis

Boys had higher unadjusted geometric mean (UGM) for PFHxS than girls (0.93 vs. 0.76 ng/mL, $p < 0.01$, Table 4). Other than this, gender did not affect UGMs for any of the other six PFAAs. Non-Hispanic whites had higher UGMs than Hispanics and non-Hispanic Asians for MPAH, PFHxS, and NPFOA ($p < 0.01$, Table 4). Also, non-Hispanic whites had higher UGMs than non-Hispanic blacks for NPFOA and MPFOS ($p < = 0.04$, Table 4).

3.2. Multivariate analysis

Boys had higher AGM than girls for MPAH (0.88 vs. 0.70 ng/mL, $p = 0.04$, Table 5) and NPFOS (2.73 vs. 2.27 ng/mL, $p = 0.04$). Non-Hispanic whites had higher AGMs than Hispanics for MPAH (0.15 vs. 0.07, $p < 0.01$, Table 5), for NPFOA (1.98 vs. 1.64 ng/mL, $p < 0.01$, Table 5), and for MPFOS (1.39 vs. 1.18 ng/mL, $p = 0.03$, Table 5). Non-Hispanic whites also had higher AGM than non-Hispanic Asians and others for PFHxS (0.99 vs. 0.63 ng/mL, $p < 0.01$) and NPFOA (1.98 vs. 1.53 ng/mL, $p < 0.01$).

Adjusted levels of NPFOS decreased with age ($\beta = -0.00422$, $p = 0.04$, Table 6). ETS exposure at indoor environments other than home was associated with higher levels of NPFOA ($\beta = 0.05142$, $p = 0.01$, Table 6). Consumption of meat other than fish and poultry was

Table 4
Unadjusted geometric means with 95% confidence intervals in ng/mL for selected perflouroalkyl acids and substances (PFAAS) by gender and race/ethnicity for children aged 3–11 years. Data from National Health and Nutrition Examination Survey 2013–2014.

	PFAAS						
	MPAH[a]	PFDE[b]	PFNA[c]	PFHxS[d]	NPFOA[e]	NPFOS[f]	MPFOS[g]
Total	0.11 (0.08 − 0.14)	0.09 (0.08 − 0.1)	0.79 (0.68 − 0.93)	0.84 (0.76 − 0.94)	1.81 (1.64 − 2.01)	2.51 (2.3 − 2.74)	1.23 (1.09 − 1.4)
Boys (B)	0.11 (0.07 − 0.15)	0.09 (0.07 − 0.11)	0.83 (0.69 − 1)	0.93 (0.81 − 1.07)	1.83 (1.65 − 2.04)	2.67 (2.33 − 3.06)	1.26 (1.08 − 1.48)
Girls (G)	0.11 (0.08 − 0.14)	0.09 (0.08 − 0.11)	0.76 (0.64 − 0.9)	0.76 (0.67 − 0.85)	1.79 (1.57 − 2.03)	2.36 (2.19 − 2.53)	1.2 (1.04 − 1.39)
Non-Hispanic White (NHW)	0.14 (0.09 − 0.21)	0.09 (0.07 − 0.11)	0.8 (0.65 − 0.99)	0.95 (0.84 − 1.06)	2.04 (1.83 − 2.28)	2.63 (2.37 − 2.91)	1.39 (1.21 − 1.6)
Non-Hispanic Black (NHB)	0.09 (0.07 − 0.13)	0.1 (0.08 − 0.12)	0.82 (0.64 − 1.05)	0.73 (0.53 − 1.01)	1.46 (1.15 − 1.85)	2.43 (1.82 − 3.24)	0.98 (0.72 − 1.33)
Hispanic (HISP)	0.07 (0.06 − 0.09)	0.09 (0.08 − 0.1)	0.75 (0.62 − 0.91)	0.79 (0.7 − 0.89)	1.61 (1.47 − 1.78)	2.29 (2 − 2.61)	1.13 (1 − 1.27)
Non-Hispanic Asian (NHAS)	0.05 (0.04 − 0.08)	0.13 (0.09 − 0.18)	0.89 (0.66 − 1.2)	0.61 (0.5 − 0.74)	1.69 (1.44 − 2)	2.94 (2.28 − 3.8)	1.2 (0.91 − 1.58)
Other (OTH)	0.13 (0.08 − 0.21)	0.11 (0.08 − 0.15)	0.77 (0.57 − 1.04)	0.73 (0.53 − 1)	1.81 (1.44 − 2.29)	2.34 (1.69 − 3.23)	1.07 (0.73 − 1.56)
Statistically Significant Differences	NHW > HISP ($p < 0.01$), NHW > NHAS ($p < 001$), NHB > HISP ($p = 0.04$), HISP < OTH ($p = 0.03$), NHAS < OTH ($p < 0.01$)	NHW < NHAS ($p = 0.03$), HISP < NHAS ($p = 0.04$)		B > G ($p < 0.01$), NHW > HISP ($p = 0.03$), NHW > NHAS ($p < 0.01$), HISP > NHAS ($p = 0.02$)	NHW > NHB ($p < 0.01$), NHW > HISP ($p < 0.01$), NHW > NHAS ($p = 0.04$), NHB < OTH ($p = 0.04$)		NHW > NHB ($p = 0.04$), NHW > HISP ($p < 0.01$)

[a] Monomethyl branch isomers of PFOS.
[b] Pefluorodecanoic acid.
[c] Perfluorononanoic acid.
[d] Perfluorohexane sulfonic acid.
[e] Linear perfluorooctanoate.
[f] Linear perfluorooctane sulfonate.
[g] Monomethyl branch isomers of PFOS.

Table 5
Adjusted geometric means with 95% confidence intervals for selected perfluoroalkyl acids and substances (PFAAS) in ng/mL for children aged 3–11 years by gender and race/ethnicity. Data from National Health and Nutrition Examination Survey 2013–2014.

	PFAAS						
	MPAH	PFDE	PFNA	PFHxS	NPFOA	NPFOS	MPFOS
Boys (B)	0.1 (0.08 – 0.12)	0.1 (0.07 – 0.12)	0.84 (0.68 – 1.05)	0.88 (0.66 – 1.18)	1.68 (1.26 – 2.24)	2.73 (1.82 – 4.11)	1.19 (0.86 – 1.67)
Girls (G)	0.1 (0.08 – 0.13)	0.09 (0.07 – 0.11)	0.76 (0.61 – 0.93)	0.7 (0.51 – 0.95)	1.63 (1.28 – 2.07)	2.27 (1.59 – 3.24)	1.15 (0.86 – 1.53)
Non-Hispanic white (NHW)	0.15 (0.1 – 0.23)	0.08 (0.06 – 0.12)	0.85 (0.67 – 1.08)	0.99 (0.76 – 1.28)	1.98 (1.59 – 2.46)	2.63 (1.92 – 3.62)	1.39 (1.09 – 1.77)
Non-Hispanic black (NHB)	0.09 (0.06 – 0.13)	0.11 (0.08 – 0.14)	0.83 (0.64 – 1.07)	0.74 (0.5 – 1.1)	1.51 (1.05 – 2.16)	2.44 (1.52 – 3.92)	1.01 (0.65 – 1.55)
Hispanic (HISP)	0.07 (0.05 – 0.1)	0.09 (0.07 – 0.12)	0.77 (0.62 – 0.97)	0.81 (0.62 – 1.08)	1.64 (1.26 – 2.15)	2.37 (1.58 – 3.55)	1.18 (0.88 – 1.58)
Non-Hispanic Asians and other unclassified race/ethnicities (NHASO)	0.1 (0.06 – 0.16)	0.1 (0.08 – 0.12)	0.75 (0.59 – 0.96)	0.63 (0.45 – 0.88)	1.53 (1.18 – 1.98)	2.52 (1.67 – 3.8)	1.15 (0.8 – 1.63)
Statistically significant differences	NHW > HISP ($p < 0.01$)			B > G ($p = 0.04$), NHW > NHASO ($p < 0.01$), HISP > NHASO ($p = 0.04$)	NHW > HISP ($p = 0.01$), NHW > NHASO ($p < 0.01$)	B > G ($p = 0.04$)	NHW > HISP ($p = 0.03$)

associated with increased levels of NPFOS ($\beta = 0.00035$, $p < 0.01$, Table 6) and MPFOS ($\beta = 0.00027$, $p = 0.02$, Table 6). However, consumption of fish was associated with decreased levels of PFDE ($\beta = -0.00058$, $p = 0.01$, Table 6) but consumption of eggs was associated with higher levels of PFDE ($\beta = 0.00105$, $p = 0.04$, Table 6). Higher levels of PFHxS were associated with consumption of fruits and juices ($\beta = 0.00019$, $p = 0.03$, Table 6).

4. Discussion

4.1. Impact of gender

Adult and adolescent males were found to have higher adjusted levels of PFHxS, PFNA, PFOA, as well as PFOS ($p < 0.01$, Jain, 2014a). Males having higher levels of PFAAs than females have been reported by other researchers also, for example, Calafat et al. (2007a, 2007b). In this study, among children, boys had higher levels of all seven PFAAs but statistically significant differences were observed for PFHxS ($p = 0.04$) and NPFOS ($p = 0.04$) only. Thus, results of this study confirm the conclusions reached by Jain (2014a) among adolescents and adults. Recently, Protano et al. (2016) reported gender differences in the urinary levels of selected trace elements among Italian school aged children which they postulated to be due to hormonal or genetic factors. It is quite possible though more work will be needed that boys having higher levels of selected PFAAs than girls may be due to hormonal factors controlling the release of these PFAAs or genetic factors responsible for absorption, distribution, retention, and excretion of these PFAAs.

4.2. Impact of race/ethnicity

Non-Hispanic whites had higher levels of all seven PFAAs except PFDE than other three race/ethnicities and quite often differences were statistically significant. Hispanics which include Mexican Americans may have lower levels than non-Hispanic whites and non-Hispanic blacks because some of the Mexican Americans who may have migrated to US recently may have been exposed to lower levels of PFAAs in Mexico. Among adults and adolescents, non-Hispanic white did have higher levels have Mexican Americans for PFNA, PFHxS, PFOA, and PFOS ($p < 0.01$) but lower levels than Non-Hispanic black for PFNA and PFOS (Jain, 2014a).

Difference in how different race/ethnicities may metabolize various toxic chemicals have been noted. For example, non-Hispanic blacks smoke lower number of cigarettes than non-Hispanic whites yet observed levels of cotinine in serum are substantially higher among non-Hispanic blacks than non-Hispanic whites (Jain, 2014b). Thus, it is entirely possible that different race/ethnicities may metabolize PFAAs differently and this may be reflected in the observed levels of PFAAs in serum.

4.3. Overall contribution of diet

Of the total variability that could be explained in the observed levels of MPAH, PFDE, PFNA, PFHxS, NPFOA, NPFOS, and MPFOS, percent variability accounted for by the dietary factors was 43.8%, 55.3%, 72.3%, 47.2%, 18.6%, 60.6%, and 26.5% for MPAH, PFDE, PFNA, PFHxS, NPFOA, NPFOS, and MPFOS respectively. Compared to this, for those aged > = 12 years, percent variability accounted for diet was 10.4% for PFHxS, 17.3% for PFNA, 21.3% for PFOA, and 15.7% for PFOS (Jain, 2014a). Proportion of variance explained by diet for children aged 3–11 years by this study was substantially higher at 47.2% for PFHxS, 72.3% for PFNA, and 60.6% for NPFOS. But, for NPFOA, percent explained variance was 18.6% for children and for PFOA, 21.3% for those aged > = 12 years by Jain (2014a). Thus, in general, diet accounts for higher percent of explained variance among children than among adolescents and adults which should not be surprising. Diet

Table 6
Regression slopes with p-values for the models for fitted for log10 transformed values of selected perfluoroalkyl acids and substances (PFAAS) in ng/L for children aged 3–11 years. Data from National Health and Nutrition Examination Survey 2013–2014.

	PFAAS used as dependent variables with log10 transformations						
Independent Variable	MPAH	PFDE	PFNA	PFHxS	NPFOA	NPFOS	MPFOS
Age	−0.00878 (0.07)	−0.00211 (0.39)	−0.00438 (0.09)	−0.00215 (0.41)	−0.00274 (0.21)	**−0.00422 (0.04)**	−0.00386 (0.07)
Age^2	−0.02748 (0.25)	0.01584 (0.12)	0.01768 (0.12)	−0.00592 (0.6)	0.01223 (0.28)	−0.00788 (0.39)	0.01244 (0.4)
Poverty income ratio	−0.00061 (0.65)	−0.00033 (0.57)	0.00025 (0.71)	−0.00026 (0.54)	−0.00031 (0.55)	−0.00036 (0.52)	0.00033 (0.6)
BMI Percentile	0.00113 (0.88)	0.00268 (0.34)	0.00588 (0.05)	−0.00374 (0.29)	0.00029 (0.93)	0.00101 (0.73)	−0.00144 (0.64)
ETS exposure at other indoor environments	0.0778 (0.46)	−0.02665 (0.58)	−0.02994 (0.49)	0.06092 (0.34)	**0.05142 (0.01)**	0.04394 (0.33)	0.04251 (0.37)
ETS exposure inside home	−0.0683 (0.52)	−0.09548 (0.14)	−0.02231 (0.74)	0.01564 (0.77)	−0.07913 (0.06)	−0.06412 (0.28)	−0.00737 (0.91)
Total caffeine intake in mg	0.00257 (0.23)	−0.00053 (0.5)	0.00072 (0.45)	0.00058 (0.38)	0.00042 (0.51)	0.00109 (0.14)	0.00061 (0.48)
Total fat intake in gm	0.00127 (0.53)	−0.0002 (0.78)	−0.00082 (0.14)	0.00043 (0.67)	−0.00019 (0.75)	0.00078 (0.36)	0.00003 (0.97)
Milk and milk products without cheese	−0.00018 (0.21)	0 (0.92)	0.00001 (0.75)	−0.00002 (0.81)	0.00002 (0.75)	0.00001 (0.9)	0.00002 (0.8)
Cheese	0.00133 (0.3)	−0.00045 (0.6)	0.00067 (0.38)	−0.00038 (0.58)	0.00026 (0.49)	−0.00068 (0.32)	0.00043 (0.53)
Meat, not fish, not poultry	0.00023 (0.44)	0.00002 (0.88)	0.0003 (0.09)	0.00018 (0.36)	0 (0.99)	**0.00035 (< 0.01)**	**0.00027 (0.02)**
Fish	−0.00062 (0.15)	**−0.00058 (0.01)**	0.00016 (0.58)	0.00009 (0.66)	−0.00009 (0.61)	0.00021 (0.35)	0.00017 (0.48)
Poultry	−0.00012 (0.79)	0.00016 (0.28)	0.00049 (0.02)	−0.00056 (0.01)	−0.00008 (0.6)	−0.00015 (0.33)	−0.00014 (0.59)
Eggs	0.00085 (0.42)	**0.00105 (0.04)**	0.00133 (0.05)	0 (1)	0.00065 (0.16)	**0.00081 (0.03)**	0.00021 (0.55)
Dry Beans	−0.00097 (0.14)	0.00062 (0.27)	−0.00002 (0.94)	−0.00004 (0.92)	−0.00021 (0.4)	−0.00019 (0.45)	−0.00017 (0.6)
Grain Products	−0.0001 (0.6)	0.00009 (0.51)	0.00015 (0.18)	0.00001 (0.9)	0.00009 (0.21)	−0.00006 (0.53)	0 (0.98)
Fruits and juices	0.0001 (0.66)	0.00002 (0.82)	−0.00001 (0.84)	**0.00019 (0.03)**	0.00006 (0.31)	0.00003 (0.65)	0.00002 (0.85)
Vegetables other than tomatoes and dark green vegetables	0.00003 (0.95)	0.00002 (0.94)	0.00015 (0.52)	0.00002 (0.92)	0.0001 (0.38)	0.00003 (0.88)	−0.00014 (0.46)
Dark green vegetables	0.00078 (0.14)	0.00046 (0.11)	−0.00037 (0.3)	0.00009 (0.67)	−0.00002 (0.87)	0.00003 (0.87)	0 (0.98)
Tomatoes	−0.00077 (0.2)	0.00031 (0.68)	0.00078 (0.08)	−0.00087 (0.15)	0.00033 (0.33)	−0.00039 (0.41)	−0.00066 (0.15)
Fats and opils	0.00244 (0.29)	0.00085 (0.65)	−0.00145 (0.17)	−0.00024 (0.81)	−0.00003 (0.92)	−0.00045 (0.67)	−0.00026 (0.73)
Sugars and sweets	0.00063 (0.51)	−0.00029 (0.44)	−0.00009 (0.72)	0.00011 (0.61)	−0.00007 (0.74)	0.00034 (0.48)	0.00035 (0.49)
Non-alcoholic beverages	−0.00005 (0.7)	−0.00007 (0.23)	−0.00009 (0.13)	−0.00009 (0.15)	−0.00003 (0.68)	−0.00009 (0.13)	−0.00007 (0.31)
Water, non-carbonated	−0.00004 (0.55)	0 (0.99)	−0.00004 (0.18)	−0.00005 (0.16)	−0.00001 (0.67)	−0.00004 (0.4)	−0.00005 (0.31)
R^2 in %	12.0	7.9	10.5	13.7	11.0	14.1	11.2
Total energy intake in KCals	0.0001 (0.43)	−0.00006 (0.23)	0 (0.94)	0.00005 (0.5)	0.00002 (0.69)	0.00006 (0.18)	0.00002 (0.75)

accounting for higher levels of explained variance may be because diet may be the predominant source of exposure to PFAAs while adolescents and adults being outside the home more often than children including for work may be exposed to several other sources of exposure to PFAAs. It should also be noted that total explained variance indicated by R^2 was 11.2% for PFNA, 14.2% for PFHxS, 11.8% for NPFOA, 14.2% for NPFOS, and 11.35 for MPFOS. Compared to this, total explained variance for adolescent and adults in the stud by Jain (2014a) was 9.9% for PFHxS, 14.6% for PFNA, 22.1% for PFOA, and 22.1%. Thus, total explained variance for children were smaller than for adolescents and adults. The reason for this is unknown. Smaller sample sizes for this study as compared to the study by Jain (2014a) may be one reason. While serum albumin, protein, triglyceride, and protein were used as independent variables in the study by Jain (2014a), they could not be used in this study because of the non-availability of the data for these 4 variables for the ages used in this study. This could be another reason.

4.4. Impact of dietary variables

Neither cheese nor milk products other than cheese were found to be associated with any of the seven PFAAs in this study for children aged 3–11 years. In the study among adolescents and adults (Jain, 2014a), use of milk products other than cheese were positively associated with the levels of PFNA ($p < 0.01$) and negatively associated with the levels of PFOA ($p < 0.01$) and PFOS ($p < 0.01$). The reasons for these discrepant results is unknown though if the milk products were contaminated with PFOA and PFOS, a positive association should be expected. It is unknown but could it be that isomers of PFOA and PFOS used for this study and PFOA and PFOS used by Jain (2014a) may have different types of associations with consumption of milk products. It should, however, be noted that there were no available data to assess if the milk products consumed by the NHANES participants were contaminated with any PFAA. Another study that may have studies the association between PFAAs and consumption of non-human milk could not be located.

Consumption of fish among adolescents and adults was found to be positively associated with the adjusted levels of PFNA and PFOS (Jain, 2014a, $p < 0.01$). In this study, neither isomers of PFOA and PFOS nor PFNA were found to be associated with the consumption of fish. Instead, consumption of fish was found to be negatively associated with PFDE levels ($p < 0.01$). It is possible that children as compared to adolescents and adults do not consume enough fish to cause elevated levels of PFOA, PFOS, and other PFAAs in serum. It is unknown if inability to separate out geographical areas with and without contamination could have skewed the results of this study.

Among children, consumption of eggs was found to be positively associated with the levels of both PFDE and NPFOS. Among adolescents and adults, consumption of eggs was not found to be a risk factor (Jain, 2014a). Could it be that children are relatively heavier consumers of eggs by body-weight than adolescents and adults? If so, a positive association among children could be expected but not necessarily so among adolescents and adults. It is also possible that non-stick cookware which contain PFAAs may be in greater use recently than they were during the time covered by the previous study (Jain, 2014a).

Consumption of fruits and juices, probably because of PFAA contamination was positively associated with the levels of PFHxS. This association was not seen among adolescents and adults probably because children may be relatively heavier consumers of fruits and juices by body-weight than adolescents and adults.

Since, PFAAs bio-accumulate, children may not have accumulated high enough levels of PFAAs to be expressed in observed levels of PFAAs in serum while adolescents and adults may have accumulated high enough levels of PFAAs to be expressed in serum and other fluids.

4.5. Impact of exposure to environmental tobacco smoke (ETS)

Exposure to ETS in indoor environments other than home was positively associated ($\beta = 0.05142$, $p < 0.01$) with the levels of NPFOA. This translates to 12.6% increase in the levels of NPFOA because of exposure to ETS in indoor environments other than home. Protano et al. (2016) reported the effect of exposure to ETS from other family members' smoking in the urinary levels of selected trace elements among school aged children in Italy. Among adolescents and adults (Jain, 2014a), smokers did have higher levels of PFNA, PFOS, PFOA, and PFHxS than nonsmokers but the differences were not statistically significant. Mechanism of how tobacco smoker constituents may affect the observed levels of PFAAs is not known.

4.6. Summary and conclusion

1. Diet is the dominant and the most important source of exposure to PFAAs among children.
2. Boys had higher levels of MPAH and NPFOS than girls.
3. Non-Hispanic white children had higher levels of selected PFAAs than Hispanic and non-Hispanic Asian and other children.
4. Exposure to ETS was associated with elevated levels of NPFOA.

4.7. Limitations of the study

While adequate information on diet and exposure to tobacco smoke, two important sources of exposure to PFAAs was available in NHANES, there are many other sources of exposure to PFAAs to which children may have been exposed and for which NHANES does not provide any data. These sources include consumption of water contaminated with PFAAs, consumption of foods cooked in non-stick cookware that may have PFAAs in their coating, levels of PFAAs in inhaled air dust inside and outside the homes, use of stain repellents, use of water-proof clothing, presence of fire-fighting foam, and transfer of PFAAs from occupational workers via air dust or clothing. It is unknown in what way the availability of information on these sources of exposure may have changed the results of this study. This constitutes a limitation of this study.

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